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U.S.-Japan Joint Meeting on the Toxicological Characterization of Environmental Chemicals of Mutual Interest*

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The paper describes deliberations of a meeting between scientists from the U.S. National Toxicology Program and the National Institute of Hygienic Sciences, Tokyo, Japan. The scientific approaches and experimental processes used by each organization in designing, conducting, and evaluating the short-term and long-term toxicity/carcinogenicity of environmental chemicals were evaluated.

Introduction

A joint meeting was held January 30 through February 1, 1989, between scientists from the U.S. National Toxicology Program (NTP), Research Triangle Park, NC, and the National Institute of Hygienic Sciences (NIHS), Tokyo, Japan, to exchange information on the scientific issues and processes involved in the design, conduct, and evaluation of both short-term and long-term toxicity/carcinogenicity studies.

As emphasized in the opening statements by Dr. Y. Omori (NIHS) and Dr. D. P. Rall (NTP), countries must work together in evaluating the toxicity of environmental chemicals in order to better protect public health throughout the world. This cooperation will minimize duplication of effort and will ensure better use of facilities, staff, and funds, hence allowing more chemicals to be evaluated more thoroughly.

Only a few of the 50,000 to 60,000 chemicals in common use have been studied adequately, and the worldwide production of synthetic organic chemicals has risen 300-fold during the last four decades. Only by countries working together can the number of chemicals evaluated be increased. Experimental evidence in the field of carcinogenesis coupled with epidemiological findings support the concept that results observed in laboratory animals can be used to predict probable results for humans. All chemicals known to induce cancer in humans that have been studied under adequate experimental conditions also cause cancer in animals (*1*). An analysis of the International Agency for Research on Cancer (IARC) Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity (*2*), indicates that approximately 1200 chemicals are currently undergoing long-term chemical carcinogenicity studies in about 88 institutes in 20 countries. Of the studies listed, approximately 315 were being conducted by the NTP and 55 by the NIHS. Formal presentations on experimental programs to characterize chemical toxicity and carcinogenicity by U.S. and Japanese participants were followed by informal discussions. Brief summaries of the presentations follow in the next sections.

U.S. National Toxicology Program

The NTP was established in 1978 by the Department of Health and Human Services (DHHS) to coordinate and integrate both basic and applied toxicology research and testing activities within DHHS. The Program is mandated to: *a*) broaden the spectrum of toxicologic information obtained on chemicals selected and evaluated; *b*) increase the number of chemicals and toxicologic end points evaluated, within resource limits; *c*) develop and validate a series of assay methods and protocols appropriate for regulatory needs; and *d*) communicate the plans and results to governmental agencies, the medical and scientific communities, and the public (*3*).

The NTP currently combines resources from three agencies within DHHS including the Centers for Disease Control (National Institute for Occupational Safety

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and Health), Food and Drug Administration (National Center for Toxicological Research), and the National Institutes of Health (NIH). The National Institutes of Health's National Cancer Institute (NCI) was a charter member agency and remains active in the Program through membership on the Executive Committee. The NCI bioassay program was transferred to NIH in 1981.

Chemicals are selected for NTP toxicology and carcinogenesis study primarily because of potential widespread human exposure and a lack of adequate toxicity data. Other selection criteria include the level of production, uses, chemical structure, physical and chemical properties, and interest by research and regulatory agencies. The chemicals evaluated are diverse with respect to use and structural classes, and include naturally occurring (32%) and synthetic (68%) chemicals (*4*). Designing and conducting toxicologic experiments on such diverse classes of chemicals requires a flexible scientific approach. Although NTP employs core protocols in terms of species, magnitude and number of dose levels, and duration of exposure (*4*), the toxicological information sought on selected chemicals takes into account a number of factors and involves a multidisciplinary approach. Table 1 outlines the sequence of events from chemical nomination to publishing results as technical reports (*4*). Detailed descriptions of the varied processes were presented and discussed at the joint meeting, and they can be found in several reports (*4–10*). Only a few major features will be summarized in this report.

Chemical Nomination and Selection

Nominations of chemicals for toxicological evaluation are submitted by member agencies of the NTP as well as by other government agencies, industry, labor, and the public. Literature summaries are prepared for each chemical, and nominations are evaluated by the multiagency Chemical Evaluation Committee (CEC), which recommends the types of studies to be considered with a testing priority rating for each chemical.

The CEC recommendations are published for comment in the *Federal Register* and are then reviewed by the NTP Board of Scientific Counselors. Final decisions on whether to continue with the evaluation or to delete chemicals nominated for various types of experiments are made by the NTP Executive Committee, composed of the Directors of the U.S. Federal health research and regulatory agencies.

Toxicology Studies Design

Following Executive Committee action, each chemical is assigned to a staff scientist who evaluates the available data and makes recommendations on experimental design. All short-term (14-day; 90-day) and long-term (2-year) toxicity study designs are reviewed by the NTP Toxicology Design Review Committee. This committee, composed of NTP staff scientists with expertise in carcinogenesis, toxicology, pathology, statistics, pharmacokinetics, genetics, animal care, and

Table 1. Chemical nomination to technical report issuance.

Identification of NTP priority chemicals	Pre-study phase	In-life study phase	Data analysis and interpretation
Chemical nomination	Select toxicologist study manager	Toxicology prechronic studies (14-day, 90-day)	Statistical analyses
Public, industry, government	Prepare health and safety document	Chemical disposition	Data interpretation and evaluation
Chemical Evaluation Committee	Procure and analyze chemical	Genetic toxicology	Draft technical report
Federal Register announcement	Develop study design	Special studies	Multidisciplinary staff review
Board of scientific counselors	Toxicology Design Committee review	In-Life audits	**Board of Scientific Counselors**
Chemical selection	Federal Register announcement	Reviews and evaluation	Peer review of draft technical report
Executive Committee	Issue request for proposal	Necropsy	Preparation and issuance of technical report
	Review proposals	Gross pathology	
	Select laboratory to perform study	Histopathology	
		Pathology quality assessment	
		Pathology working group	
		Federal Register announcement	
		Develop study design for toxicology and carcinogenesis studies	
		Toxicology and carcinogenesis studies (2-year and special studies)	
		In-life audits	
		Review and evaluation	
		Necropsy	
		Gross pathology	
		Histopathology	
		Pathology quality assessment	
		Pathology working group	
		Data audits	

health and safety, evaluates and then approves or modifies the study design.

In some instances, a study is designed to focus on a specific toxicological end point, but ordinarily the goal is a comprehensive toxicological characterization of the chemical including metabolism and disposition, genetic toxicity, fertility and reproductive assessment, carcinogenicity, and other toxic effects on specific target organs (e.g., immune or nervous system). Toxicologic characterization usually includes 14-day and 90 to 120 day studies, followed in many cases by 2-year studies. Studies are performed under contract to the NTP by qualified private laboratories or by another government agency or national laboratory. All of these studies are carried out under Good Laboratory Practices (GLP).

Chemical Pathology

Since pathology data often provide the end point for decisions concerning the potential hazards of a chemical, it is essential that such data be accurate and reflect current knowledge of laboratory animal pathology. Both qualitative and quantitative pathology diagnoses must be considered. In typical 2-year carcinogenesis studies, 20,000 to 40,000 tissue sections are made for each chemical studied in both sexes of rats and mice. When the laboratory pathology evaluation is completed, the slides, individual animal data, and pathology tables are evaluated by an independent pathology quality assessment laboratory.

The quality assessment report and representative slides are subsequently reviewed by an ad hoc Pathology Working Group (PWG) composed of experienced members in rodent pathology, and the final diagnoses represent a consensus of study laboratory, quality assessment, and PWG pathologists (*11*). This procedure has worked very successfully for the NTP and helps assure that the pathology aspects of the study are consistently evaluated.

Data Evaluation, Peer Review, and Dissemination

The principal statistical methods employed in NTP toxicology/carcinogenesis studies include survival analysis and mortality-adjusted evaluation of tumor incidence (*12*). Although the statistical significance of an observed tumor increase is an important piece of evidence used in the evaluation process, other issues such as biologic significance, experimental design and conduct, false positives/false negatives, increasing/decreasing trends in tumor incidence, and the use of historical controls are also considered. Rigid statistical rules are not employed in the interpretation of carcinogenicity data, and biological mechanisms are always considered.

The quality assurance of data is an integral component of NTP toxicity/carcinogenicity studies. Good Laboratory Practices compliance inspections and in-life (and retrospective) data audits are conducted in contract laboratories. No formal conclusions or technical reports are issued until a retrospective audit has been completed.

The NTP uses the following five categories of evidence of carcinogenic activity to summarize the results observed in each experiment (male mice, female mice, male rats, female rats).

a) Clear evidence of carcinogenicity is demonstrated by studies that are interpreted as showing a dose-related increase of malignant neoplasms, increase of a combination of malignant and benign neoplasms, or marked increase of benign neoplasms if there is an indication from this or other studies of such tumors to progress to malignancy.

b) Some evidence of carcinogenicity is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

c) Equivocal evidence of carcinogenicity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.

d) No evidence of carcinogenicity is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.

e) Inadequate study of carcinogenicity is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of a carcinogenic activity.

These categories refer to the strength of the experimental evidence and not to carcinogenic potency or mechanism.

Scientific peer review is a fundamental component of the NTP program. Draft technical reports summarizing and evaluating the data on each chemical are peer-reviewed first by staff, then in public meetings by a Peer Review Panel of experts in chemical carcinogenesis. The recommendations of the reviewers and relevant comments recorded at the meeting are incorporated in the final revision of the Technical Reports. NTP actively disseminates its reports both nationally and internationally.

National Institute of Hygienic Sciences, Japan

The National Institute of Hygienic Sciences (NIHS) was established in 1874 as the Tokyo Drug Control Laboratory in Tokyo. It is the oldest research Institute that belongs to the Ministry of Health and Welfare (MHW). At the very beginning, the NIHS was principally engaged in the inspection of the quality of imported drugs and of the chemicals in foods and water (including hot spring water). However, with the increasing concern of the public over the safety of a variety of chemicals, the

need for toxicological studies, in addition to physicochemical studies, became very apparent.

Under these circumstances, in 1978, an organization called the Biological Safety Research Center (BSRC) was established together with a new building and animal facilities in the NIHS. The BSRC consists of four divisions, namely, Division of Toxicology (Head, Y. Kurokawa), Division of Pharmacology (Head, A. Takanaka), Division of Pathology (Head, Y. Hayashi), and Division of Mutagenesis (Head, M. Ishidate, Jr.) under the Director of BSRC (M. Tobe). Approximately 60 professional staff and 20 professional technicians are working at the BSRC. There are 13 other divisions in the NIHS under the Director General (A. Tanimura) and the Deputy Director General (M. Uchiyama) in addition to the Divisions of the BSRC.

Toxicological Studies at the BSRC

The BSRC conducts various toxicological studies as a laboratory arm of the MHW, especially for the Ministry's Pharmaceutical Affairs Bureau and the Environmental Health Bureau. High priority chemicals to be studied at the BSRC are selected on the basis of public concern over human health. Usually the amount of production and use, biological and environmental effects, and the quality and quantity of previous toxicological data are considered before the final decision. The chemicals to be selected include medical drugs, food additives, agrochemicals, existing or new chemicals and household chemicals which are regulated, respectively, under the Pharmaceutical Affairs Law, Food Sanitation Law, Agricultural Chemical Regulation Law, Chemical Substances Control Act, and Household Chemicals Control Act. Also relevant are the Poisonous and Deleterious Substances Control Law and the Industrial Safety and Health Law. GLP standards have been applied for toxicity testing of medical drugs, agrochemicals, and existing or new chemicals since the early 1980s. The toxicity tests required for the safety evaluation of each category of chemicals are shown in Table 2.

So far, approximately 900 chemicals or mixtures have been examined at the BSRC by various *in vivo* and/or *in vitro* toxicological tests. The numbers of each test conducted are listed in Table 3. A total of 453 *in vivo* studies including 87 carcinogenicity tests has been conducted mainly by feeding (42%) or by gavage (31%). Others are by drinking, skin application, subcutaneous injection, inhalation, etc. As to test species, the rat (F344, Wistar, Sprague-Dawley) has been the most frequent one used, followed by the mouse (B6C3F1, ddY), rabbit, guinea pig, monkey, dog, and hamster. On some occasions, the tests required by the BSRC are conducted at outside facilities (universities, local Public Health Institutes, contract laboratories).

The test results obtained at the BSRC are submitted to the MHW as a Final Report, and raw data are also offered for further reference when required. The Final Report is examined by the officials of responsible divisions of the bureau and is used as scientific background data for their political management. Some of the Final Reports are also opened for discussion at the council for drugs, food, and others to obtain expert opinions before any final regulatory decision is made by the MHW.

Table 2. Toxicity tests and GLP in relation to chemical class and regulatory law.[a]

	Drugs	Food additives	Agro chemicals	Chemicals	Household chemicals
Regulatory law/test	Pharmaceutical affairs Law (1987)	Food Sanitation Law (1965)	Agricultural Chemical Regulation Law (1972)	Chemical Substances Control Act (1974)	Household Chemicals Control Act (1974)
Acute	R	R	R	MBR	ND[b]
Subacute	R	MBR	R	NR	NR
Chronic	R	R	R	R	ND
Reproduction	NR	R	R	R	ND
Teratology	R	R	R	R	ND
Dependence	MBR	NR	NR	NR	NR
Antigenicity	MBR	NR	R	NR	ND
Mutagenicity	MBR	R	R	R	ND[c]
Carcinogenicity	MBR	MBR	R	R	ND
Local irritation	MBR	NR	R	NR	ND
28-day repeated	NR	NR	NR	R[c]	NR
Delayed neurotoxicity	NR	NR	MBR	NR	NR
GLP	R (1983)	NR	R (1984)	R (1984)	NR

[a] R, required; NR, not required; MBR, may be requested; ND, requirement not determined.
[b] Poisonous & Deleterious Substances Control Law (1965).
[c] Industrial Safety & Health Law (1972).
[d] Screening toxicity test.

Table 3. Numbers of toxicity tests conducted at the biological safety research center (BSRC), NIHS since 1976.

Test	Number
Acute toxicity	148
Subacute toxicity	40
Subchronic toxicity	72
Chronic toxicity	63
Carcinogenicity	87
Two-stage carcinogenesis (skin, stomach, liver, kidney, pancreas)	63
Organ toxicity (skin, kidney, lung, heart, eye)	25
ADME (absorption, distribution, metabolism, excretion)	49
Teratogenicity	43
Multigeneration	3
Synergy	8
Allergy	3
Ames test	134[a]
Chromosome aberration test	781
Micronucleus test	46

[a] Positive tests only.

At the BSRC, the following 17 chemicals will be tested or are being tested for chronic toxicity/carcinogenicity using rats or mice:

- dicofol
- bis(tributyltin) oxide
- dipentene dimer
- 1-cyanoguanidine
- 1,1-bis(*tert*-butylperoxy)-3,3,5-trimethylcyclohexane
- 5-chloro-2-methyl-4-isothiazolin-3-one
- potassium pyrophosphate
- sodium polyacrylic acid
- aluminum potassium sulfate
- cochineal
- phytic acid
- capsaicin
- tannic acid
- tragacanth gum
- phloxine
- gardenian color (yellow)
- carrageenan

Also, mutagenicity and 28-day toxicity studies are being done on seven chemicals under the Chemical Substances Control Act: nitrobenzene, dicyclopentadiene, diphenylamine, pigment blue 15, chlorocyclohexane, pentaerythritol, and benzene-1,2-decarboxylate diheptyl.

Chemical Substances Control Act

This law was adopted in Japan in 1973 to strictly regulate chemicals that have properties of persistence and bioaccumulation and potential chronic toxicological effects that may be hazardous to humans. Until now, nine chemicals have been designated by Cabinet order as Specified Chemical Substances (i.e., PCB, PCN, HCB, aldrin, dieldrin, endrin, DDT, chlordane and heptachlor). However, in 1986 this law was revised to include chemicals that show properties of persistence but relatively low bioaccumulation (e.g., trichloroethylene). The new concept follows: *a*) Chemicals that do not accumulate in bioorganisms but have persistence and the potential to be harmful shall be designated as "Designated Chemical Substances," whose quantity of manufacture or import should be reported to the competent authority. *b*) Any one of the "Designated Chemical Substances" that prove to threaten environmental pollution and human health by a postmarketing surveillance shall be designated as a "Class-2 Specified Chemical Substances." *c*) The "Class-2 Specified Chemical Substances" shall be permitted for manufacture and import within a certain quantity of the "Class-2 Specified Chemical Substances" in question, if it causes environmental pollution and human health injury. *d*) "Specified Chemical Substances" defined by the old Law correspond to the "Class-1 Specified Chemical Substances" in the amended Law. Accordingly, the biodegradability test for persistence, *n*-octanol/water partition coefficient test for bioaccumulation and mutagenicity tests (gene mutation and chromosomal aberration) and 28-days repeated dose toxicity tests in animals as the screening toxicity tests were adopted for new chemicals. On the other hand, so-called "Full-scale Toxicology Tests" that are required mainly for existing chemicals, chronic toxicity, carcinogenicity, reproduction, teratogenicity, toxicokinetics, mutagenicity tests *in vitro* and *in vivo*, and pharmacological tests, are conducted. However, if a chemical is not persistent, the bioaccumulation test or the toxicity test shall not be required.

The revised law came into force on April, 1987, and the Safety Evaluation Committee of the MHW has evaluated 232 chemicals (204 new and 28 existing chemicals) to date. Among them, 32 chemicals have been classified as "Designated Chemical Substances" (Table 4). It should be mentioned that as of April, 1989, trichloroethylene, tetrachloroethylene, and carbon tetrachloride have been designated as "Class-2 Specified Chemical Substances" by the government.

Priority List Issued by the MHW

In 1988, a priority list consisting of 393 chemicals was issued by the MHW for identifying candidate existing chemicals for "Designated Chemical Substances." The chemicals selected are those that have already been determined by the Ministry of International Trade and Industry (MITI) to be persistent in the environment and to have low bioaccumulative properties. They are then divided into five groups, mainly based on toxicity data taken from the Registry of Toxic Effects of Chemical Substances and some from the U.S. NTP (chemicals in group 1 have the highest priority, and those in group 4 have the lowest priority). Chemicals in Group 5 are those for which appropriate toxicity data are not available. Toxicity data examined include outcomes from carcinogenicity, mutagenicity, reproductive/developmental toxicity, and general toxicity tests.

Priority List and Survey by the Environmental Agency of Japan

Since 1979 the Environmental Agency of Japan (EAJ) has been conducting a comprehensive survey of chem-

Table 4. Designated chemical substances (since April, 1987).

Chemical substances	Mutagenicity		Animal toxicology
	Ames	Chromosome	
Trichloroethylene	±	−	+
Tetrachloroethylene	−	−	+
Carbon tetrachloride	−	−	+
Chloroform	±	−	+
1,2-Dichloroethane	+	+	+
1,4-Dioxane	−	−	+
3,3′-Dichlorobenzidine	+		+
4,4′-Diamino-3,3′-dichlorodiphenylmethane	+	+	+
2,4-Dichloro-3-methylphenol[a]	−	+	+
Sodium 4-(2,4-dichloro-m-toluoyl)-1,3-dimethylpyrazol-5-olate[a]	−	−	+
1,2-Dichloropropane	±		+
4-Methoxy-2,2′,4′-trimethyldiphenylamine[a]	−	−	+
Tributyltin methacrylate	−	−	+
bis(Tributyltin) fumarate	−	−	+
Tributltin fluoride	−	−	+
bis(Tributyltin) 2,3-dibromosuccinate	−	−	+
Tributyltin acetate	−	−	+
Tributyltin laurate	−	−	+
bis(Tributyltin) phathalate	−	−	+
Alkyl(C = 8)acrylate-methyl methacrylatetributyltin metacrylate-copolymer	−	−	+
2,2,3-Trichloro-3-phenyl-1,1-propanediol[a]	−	+	+
N,N′-Ethylenbis (salicylideneaminate) copper (II)[a]	−	−	+
Triphenyltin *N,N*-dimethyldithiocarbamate	−	−	+
Triphenyltin fluoride	−	−	+
Triphenyltin acetate	−	−	+
Triphenyltin chloride	−	−	+
Triphenyltin hydroxide	−	−	+
Triphenyltin fatty acid (C = 9-10) ester	−	−	+
Esterification product with 2-ethylhexanol at terminal carboxy groups of polycondensate (degree of polymerization: 1-100) of adipic acid•2-butyl-2-ethyl-1,3-propane-diol•1,6-hexanediol[a]	−	−	+
4-Phenoxyphenol[a]	−	+	+
Epoxidized product of 2,2-bis (hydroxymethyl)-1-butanol•1,2-epoxy-4-vinylcyclohexane adduct (degree of adduct: 1-700)[a]	−	+	+
Methyl 3,3-dimethyl-4-pentenoate[a]	−	+	+

[a] New chemical substances (animal toxicology for 28 days).

icals in the environment, independent of the MHW. The survey is based on their own priority list, issued in 1978, of 2000 existing chemicals, using the criteria of persistence, bioaccumulation, and chronic toxicity. This survey is conducted through the following three stages: In the first stage chemicals expected to have a high probability of persistence in the environment are selected (ca. 50/year). In the second stage, an environmental survey is conducted on these chemicals, and those showing persistence in the environment are chosen (ca. 5/year) for further evaluation. In the third stage, chemicals that should be handled with care are chosen from those persistent in the environment (1-2/year), and wildlife monitoring will be conducted on these chemicals. In 1987 MITI issued the revised priority list of 1145 chemicals, classified into 12 groups according to their chemical structure. In this manner this survey has been performed as a part of the safety check program for existing chemicals which are not regulated by the examination system of the Chemical Substances Control Act.

Future Perspectives at the BSRC

The greater the increase in the numbers of chemicals in the environment, the more toxicity tests are required for safety evaluation. Actually some of the tests that would be conducted at the BSRC are transferred to outside facilities when available because of the lack of manpower, animal facilities, etc., at BSRC. Therefore a movement toward establishing a new system regarding chemical selection, toxicity testing, reporting, and evaluation is now in progress. In short, it can be called a modified Japanese-NTP, since the idea is very similar to the existing and very active U.S. NTP.

Briefly, an Advisory Committee on the selection of priority chemicals for testing will be organized at first. When chemicals are nominated, the BSRC will determine the protocols for testing that will be conducted by the contract laboratories that are under strict GLP regulation. On the other hand, the BSRC will focus on conducting further fundamental studies on the toxicological mechanisms of chemicals that may have a high

probability of affecting human health. The data from the outside sources will be collected at the BSRC for inspection by the Quality Assurance Unit and will then be evaluated by the Peer Review Committee, which consists of the BSRC staff as well as outside expertise. In fact, a new division tentatively called the Division of Comprehensive Evaluation will be responsible for the overall processes of the new system; it is being planned at the BSRC and will be started in the near future. The Final Report will be submitted to the MHW and then published in the scientific journals as soon as possible to be used by various organization in the world for safety/risk assessment.

In conclusion, we believe that close communication between NIEHS and the NIHS/BSRC is necessary to exchange up-to-date toxicological information. For that purpose, annual U.S.-Japan Joint Meetings by the professional staff of the two institutes will be highly beneficial.

Concluding Remarks

Dr. Y. Omori and Dr. D. P. Rall noted in their closing remarks that the meeting had been very productive. Through both formal presentations and informal discussions, much information was exchanged about the respective programs of the NIHS and the NTP. Particular emphasis was placed on the similarities and differences in the approaches used by the two institutes. It was evident that although differences in the governmental organization and regulatory frameworks in each country resulted in unique national aspects (e.g., chemical selection procedures), the NIHS and NTP share many common objectives and methodologies in identifying the potential toxicity of a large variety of chemicals. The two countries will continue their joint efforts and avoid unnecessary duplication of effort. Priority lists of chemicals have been and will continue to be exchanged and examined in order to make recommendations to the respective national governments and international organizations on the need for toxicological evaluations of certain chemicals. Future joint meetings will continue to explore how best to implement collaborative efforts on the toxicological characterization of environmental chemicals of mutual interest.

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